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MEETING HIGHLIGHTS

Highlights of the 2003 Scientific Sessions of the Heart Failure Society of America

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Peter Liu, MD,* Marvin A. Konstam, MD,† Thomas Force, MD†‡

Toronto, Canada; and Boston, Massachusetts

The Annual Scientific Meeting of the Heart Failure Society of America (HFSA) brings together health care professionals who are dedicated to improving the diagnosis, treatment, and quality of life for individuals affected by heart failure (HF). During the 2.5-day meeting, attendees had an opportunity to hear about the latest developments in research (both basic and clinical), learn about the latest technologies used to treat HF, attend small "how to" sessions on focused topics, and hear about the latest clinical trials and guidelines. The attendance at this year's 7th annual meeting broke a new record with 3,400 registrants, compared with 2,500 registrants for last year. This is a testament of the success of the meeting in addressing the needs of this dedicated community. The meeting had over 30 sessions and obviously not all can be highlighted. This paper provides an overview of four clinical sessions, as well as the basic science portions of the scientific program.

OPENING PLENARY SYMPOSIUM—HEART FAILURE 2003: FROM CELLS TO POPULATION

Stem and progenitor cells for repair. Dr. Michael Schneider (Baylor College of Medicine, Houston, Texas) opened the plenary symposium on the topic of stem and progenitor cells for cardiac repair. Intrinsic cardiac restorative growth is *too meager* to match the demands after acute cell death in myocardial infarction (MI) or chronic sporadic cell death in HF. Currently, a variety of cell types show promise for myocardial regeneration, although the biologic understanding of this process is still primitive. *Skeletal muscle cells* have been used in clinical trials. They improve ventricular function, but without transdifferentiating into cardiomyocytes or connecting with cardiomyocytes, and are a source of arrhythmias. *Bone marrow-derived cells*—hematopoietic and mesenchymal stem cells and circulating endothelial progenitor cells or hemangioblasts—are also promising as sources of autologous cells. The phase I trials to date are encouraging, but it is unclear whether benefits are related to myocyte formation or, alternatively, to angiogenesis or an altered remodeling process. Human *embryonic stem cells* have the best proven ability to form all cell types and hold tremendous promise for therapy, but studies on these cells have been limited by religious or ethical objections.

Therefore, the most intriguing question is whether the heart actually has its own *reservoir of repair cells* that might be exploited to replace damaged myocardium more effectively. The answer appears to be "yes," and the possible candidates to date are the side-population (SP) cells, c-kit+ cells, and Sca-1+ cells. Dr. Schneider's laboratory has focused on the latter, identified using the Sca-1 marker (stem cell antigen-1). These are small interstitial cells that express many cardiac transcription factors, but not cardiac structural genes, and are viewed as predisposed to convert into cardiac muscle itself. This can be triggered in cell culture by using a drug (azacytidine), partly dependent on a receptor for growth factors with known importance for cardiac development in the embryo, called "bone morphogenic proteins." Given systemically, cardiac Sca-1+ cells home specifically to the infarct border zone and differentiate efficiently in vivo.

The future challenge for stem cell research will be to focus on stem cell mobilization and stem cell engineering, in an attempt to identify control systems for proliferation, differentiation, myocyte connectivity, and ultimately organ function and host survival.

Cellular apoptosis and survival in HF. Dr. Richard Kitsis (Albert Einstein College of Medicine, Bronx, New York) then presented a discussion on cell survival and apoptosis. The ability to prevent apoptosis or programmed cell death, particularly in ischemia-reperfusion, will have important salutary effects on HF development. During a typical infarction, 5% to 30% of myocytes in the infarct zone and 0.1% to 0.3% in the remote zone undergo apoptosis. This is in contrast to the baseline apoptosis rate of 0.01% to 0.001% in the normal myocardium. Apoptotic pathways in myocytes can be triggered by death receptor signals coupled to procaspase-8. Additional triggers can arise from an extracellular stimulus that activates Bax and releases cytochrome-c from mitochondria. This, in turn, activates Apaf-1 and procaspase-9 and, together with caspase-8, leads to caspase-3 activation and execution of cell death. In the setting of ischemia-reperfusion, inhibition of apoptosis,

From the *Heart and Stroke/Richard Lewar Centre of Excellence, University of Toronto, and Division of Cardiology, Toronto General Hospital, University Health Network, Toronto, Canada; †Division of Cardiology, and the ‡Cardiomyocyte Biology Laboratory of the Molecular Cardiology Research Institute, Tufts–New England Medical Center and Tufts University School of Medicine, Boston, Massachusetts.

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using genetic manipulations, reduces the infarct size by 50% to 60% and improves cardiac function. Similar results are obtained with the newer caspase inhibitors, where sustained reductions in infarct size and improvements in cardiac function are observed, even when administration of the drug is delayed 1 h from the onset of ischemia.

Does apoptosis directly contribute to HF? Conditional activation of a caspase gene in the mouse myocardium leads to cardiomyopathy. Conversely, inhibition of apoptosis with caspase inhibitors improves cardiac dysfunction and reduces mortality in several models of HF. Thus, at least in rodent models, there is a causal link between apoptosis and HF.

So could anti-apoptosis therapies be used to treat acute MI (ischemia-reperfusion) and chronic HF? Given long-term safety concerns associated with chronic apoptosis inhibition, the first realistic clinical target for apoptosis inhibition is likely to be acute ischemia-reperfusion. Later, it may be possible to assess the risk/benefit ratio of apoptosis inhibition for chronic HF. In either case, it may be possible to combine anti-apoptosis inhibition with the cell-based therapy discussed earlier.

Clinical cell therapy in the HF patient. Dr. Richard Weisel (University of Toronto Faculty of Medicine, Toronto, Canada) provided an overview of clinical developments in clinical applications of regenerative medicine to date. The pioneering efforts of *skeletal myoblast* transplantation has led to ventricular arrhythmias in 4 of 12 patients, requiring placement of an implantable cardioverter-defibrillator, but the cells improved regional wall motion, even though they did not beat with the surrounding myocytes. The major clinical issues to resolve are the modes of delivery of cells: intracoronary, endocardial, or the novel approach of using coronary venous access to deliver cells into the mid-myocardium of the infarct region.

Currently, the most promising sources of *stem cells* or *progenitor cells* are from the *bone marrow* or the *heart*. Successful implantation improved myocardial perfusion to the ischemic region and prevented dilation of the ventricle. The other challenges are the optimal cell types, the timing of engraftment, and how to improve the survival of the graft. The combination of the cells with gene transfer of survival factors may be a promising approach.

Future approaches to the cellular remodeling may include surgical resection, such as that being tested in the Surgical Treatment for Intra-Cerebral Hemorrhage STICH trial, together with a cellular patch graft into the infarct zone. The salutary mechanisms of these cellular grafts likely reside in their ability to increase matrix metalloproteinases and decrease their inhibitors (tissue inhibitors of metalloproteinase [TIMP]). This leads to stabilization of matrix, cell preservation, prevention of apoptosis, improvement of angiogenesis, and ultimately improvement in cell survival.

Map for the future care of patients with HF. Dr. Harlan Krumholz (Yale University, New Haven, Connecticut) expressed concern about the state of the health care system for our HF patients, as it is currently unsafe, ineffective, inequitable, inefficient, and non–patient-centered. We need to rapidly evolve to a safe and patient-centered health care system to deliver better care to our patients.

To do so, we first need to *expand our knowledge base*. We need new insights from efficacy trials to effectively prevent HF; we need new information on means of delivering effective clinical care to prevent HF. We need to have knowledge of what treatments actually improve outcomes, as well as what systems to implement to maximize benefit and efficiency.

We also need knowledge derived from *outcomes research*, generating evidence that can support clinical decision-making, improve clinical practice, and guide health policy. How are we doing now, and how can we do it better? Currently, there is no national surveillance database for HF. We need to have ongoing monitoring of HF outcomes, along with associated costs, manpower, and other resources required. For example, disease management can achieve a 26% reduction in the relative risk of combined mortality and morbidity for the HF patient. However, it is not seen as a priority within the medical community. Indeed, HF care interdisciplinary teams are at the leading edge of this concept of care, but the health care system must appreciate the value of this paradigm and accommodate this change in concept.

To move health care to the next level, we also need to practice *preference sensitive care*, whereby a patient's personal choices, such as tradeoffs in quality versus quantity of life, must be individually decided. We also need to practice *resource sensitive care*, whereby the balance of societal, community, and individual patient needs is carefully weighed, and efforts toward increased standardization of access and expenditure should be made.

We need to realize the need to change and take actions to change the culture of our health care system. We must recognize the need for change, seek ways to improve our outcomes, and move from a paradigm of *individual maverick physician* to *integrated teams*. We can enhance system performance through a concerted effort, and this is not a sign of weakness or a threat to the science and art of medicine. We need to start now.

BASIC SCIENCE SYMPOSIUM

The inaugural Basic Science Symposium on Sunday focused primarily on the role of regulators of gene transcription in normal and pathologic growth of the heart. Presentations by Dr. Eric Olson (Keynote Address; University of Texas, Southwestern Medical Center, Dallas, Texas) and Dr. Jonathan Epstein (University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania) helped clarify seemingly contradictory reports on the role of histone de-acetylases (HDACs) in regulating cardiac hypertrophy. The HDACs are enzymes that remove acetyl groups from histones, proteins associated with deoxyribonucleic acid (DNA). De-acetylation of histones blocks gene transcrip-

tion, and thus HDACs are negative regulators of transcription. In the heart, HDACs were initially identified as inhibitors of hypertrophy, as deletion of HDAC-5 and -9 in the mouse led to spontaneous hypertrophy. Similarly, Joan Heller Brown's work with a transgenic mouse expressing CaMKIIδ_B, a protein kinase that, when activated by hypertrophic stimuli, leads to the export of class II HDACs from the nucleus, thus inactivating them, also suggests a critical role for HDACs in blocking hypertrophy, as her mouse also had spontaneous hypertrophy. However, pharmacologic inhibitors of HDACs, which might have been predicted to mimic the phenotype of the knockouts and to increase hypertrophy, have recently been reported to block hypertrophic growth in cardiomyocytes in culture. The Olson and Epstein laboratories have found that these seemingly contradictory results may relate to the fact that HDAC-5 and -9, which are class II HDACs, repress transcription of prohypertrophic gene programs, whereas class I HDACs may repress transcription of antihypertrophic genes. This selectivity may be mediated, at least in part, by a protein called Hop (homeodomain only protein), which recruits class I HDACs specifically to antihypertrophic genes regulated by the transcription factor called serum response factor. In agreement with this, a transgenic mouse expressing Hop in the heart has severe hypertrophy and fibrosis and dies suddenly. Importantly, trichostatin A, an HDAC inhibitor, blocked isoproterenol-induced hypertrophy. Because HDAC inhibitors are currently in clinical trials for cancer and appear to be well tolerated, this sets up the possibility of employing HDAC inhibitors as potentially very important antihypertrophic therapies. However, class- or isoform-specific inhibitors may be required.

The study of cardiac development has largely focused on genetic determinants. In a departure from the main theme of the session, Dr. Scott Fraser (California Institute of Technology, Pasadena, California) reviewed emerging evidence that intracardiac fluid forces function as an epigenetic factor to critically regulate embryonic development of the heart. Fraser and his co-workers have used remarkable in vivo imaging technologies to demonstrate high levels of shear forces and vortical flow in the developing zebrafish heart, which is approximately the size of a coarse human hair. They found that the levels of shear forces were well above the threshold for induction of gene expression in studies of endothelial cells in culture. By physically interfering with inflow or outflow of the heart at 37 h after fertilization, they were able to test the hypothesis that these shear forces might modulate embryonic development of the heart. They found that the reduction in shear stress led to a failure of one of the chambers of the heart to develop, a failure of the heart to loop (a necessary step in cardiac development), collapse and fusion of the walls of the inflow and outflow tracts, and abnormal valve development. These studies demonstrate that direct interference with intracardiac fluid forces has profound effects on valve formation, chamber differentiation, and organ morphology. Because approximately 40% of congenital heart defects involve a valvular abnormality, these studies raise the possibility that these valvular abnormalities worsen the phenotype of the birth defect via altering intracardiac fluid forces.

Dr. Michael Schneider (Baylor College of Medicine, Houston, Texas) in the Sunday Morning Symposium, and his fellow, Dr. Motoaki Sano (finalist in the Jay Cohn New Investigator Award Basic Science competition), presented data implicating two novel pathways in the regulation of cardiac hypertrophy and cardiomyocyte apoptosis. One of these involves a cyclin-dependent kinase, Cdk9, which plays a role in activating ribonucleic acid polymerase II, an essential element in the basal machinery for transcription of genes. They reported that kinase activity of Cdk9 (and the related Cdk7) was increased in the hearts of patients with dilated cardiomyopathy. To evaluate the significance of this, they studied a transgenic mouse expressing the Cdk9 activator, cyclin T1. The mouse demonstrated spontaneous hypertrophy, but after imposition of a pressure load, left ventricular (LV) contractility deteriorated, and the mouse died within a few weeks. These studies suggest that the increased activity of Cdk9 in the failing human heart may play a role in the progression of HF and thus could serve as a novel target in the treatment of the disorder.

The second pathway involves the DNA damage-sensing protein kinase, checkpoint 2 (Chk2), which Schneider and co-workers have found to be markedly activated in the hearts of patients with advanced HF. Furthermore, this kinase is also activated by imposition of an acute pressure load (aortic banding) in the mouse. Schneider presented evidence that activation of Chk2 may play a significant role in the enhanced apoptosis seen in the failing heart. This is surprising, because this pathway has been believed to primarily function in cycling cells, not terminally differentiated cardiomyocytes. In addition, the findings identify this pathway as a possible therapeutic target to block apoptosis in patients with HF.

Dr. Helmut Drexler (Hannover Medical School, Hannover, Germany) has previously reported that signaling down the JAK/STAT pathway is down-regulated in patients with advanced HF. This pathway is activated by cytokines, growth factors, and some vasoactive peptides, including angiotensin II. Drexler presented his group's analysis of the phenotypes resulting from cardiac-specific deletion in mice with STAT3 (signal transducer and activator of transcription 3), a transcription factor that induces gene expression after cytokine stimulation. The most striking phenotype of this mouse was marked impairment of angiogenesis. In addition, the mouse had depressed systolic function and late development of HF, which was significantly accelerated by pregnancy. These findings indicate a critical role for STAT3 and the JAK/STAT pathway in cardiac angiogenesis and in the maintenance of LV function.

BASIC SCIENCE: GENERAL SESSIONS

Regulating myocardial growth, survival, and function. Dr. Kenneth Walsh (Boston University School of Medicine, Boston, Massachusetts) and his postdoctoral fellow, Dr. Ichiro Shiojima (winner of the Jay Cohn New Investigator Award for Basic Science), in their study of a mouse, presented striking findings that tell us about the reversibility of hypertrophic responses of the heart. In this mouse, expression of the prohypertrophic/anti-apoptotic protein kinase, Akt, can be suppressed by doxycycline and induced by withdrawing the drug. Short-term induction of Akt (for two weeks) led to a 70% increase in heart weight, which, remarkably, completely reverted to baseline within three days of turning off Akt expression with doxycycline. Prolonged induction (six weeks) induced marked cardiac hypertrophy with severe cardiac dysfunction, and turning off Akt expression at this point led to a further decline in contractility. These studies demonstrate remarkably rapid reversibility of short-term hypertrophy (though the molecular mechanism is not known at this point) and also suggest an important role for Akt in maintaining contractility in hypertrophic/failing hearts.

Dr. John Kyriakis (Tufts University School of Medicine, Boston, Massachusetts) has identified a new mechanism by which growth-promoting stimuli lead to entry of cells, including vascular smooth muscle cells, into the cell cycle. This involves a novel pathway in which a protein kinase, mixed lineage kinase-3 (MLK-3), is essential for both activation of the mitogen-activated protein kinases and entry into the cell cycle by growth-promoting stimuli. These data have important implications for the treatment of disorders that involve unrestrained growth of vascular smooth muscle cells and other cells, including restenosis after percutaneous coronary intervention (PCI). Furthermore, they establish MLK-3 as a potential target for therapy to block post-PCI restenosis.

Novel therapeutic strategies in HF. Dr. Elizabeth Murphy (Duke University School of Medicine, Durham, North Carolina) outlined potential approaches to blocking apoptosis in ischemic syndromes and in the hearts of patients with HF, using inhibitors of caspases and of molecular components upstream of caspase activation. Dr. Min Nian (University of Toronto, Toronto, Canada) discussed in detail one of these putative targets, cFLIP, in her presentation for the Jay N. Cohn New Investigator Award competition.

Dr. Douglas Mann (Baylor College of Medicine, Houston, Texas) reviewed recent data to help clarify the molecular mechanisms which may have accounted for the failure of anticytokine therapies targeting tumor necrosis factor-alpha with etanercept (RENEWAL) and infliximab (ATTACH) to improve outcomes in chronic HF patients, as well as the mechanisms by which these therapies worsened HF in patients in the trials.

Molecular imaging. Dr. Mike Modo (Institute of Psychiatry, London, United Kingdom) reviewed his group's work on serial in vivo imaging of transplanted stem cells with magnetic resonance imaging. Using his work on the brain as an example, he highlighted the importance of being able to track the migration, survival, proliferation, and differentiation of stem cells after their injection into diseased regions, so that these could eventually be correlated with functional recovery (or lack thereof).

Metabolic dysregulation in HF. Dr. David Carling (Imperial College, London, United Kingdom) reviewed recent progress in the regulation and function of a protein kinase that is believed to be a central sensing mechanism to protect cells in the setting of adenosine triphosphate (ATP) depletion, such as occurs with ischemia or intensive exercise. This kinase, the adenosine monophosphate (AMP)-activated protein kinase, AMPK, has become of major interest to the pharmaceutical industry, as it is believed that activators of it may be of benefit in the treatment of patients with metabolic syndrome, diabetes, and hyperlipidemia. Mutations in AMPK lead to familial hypertrophic cardiomyopathy, originally identified by Dr. Hugh Watkins and co-workers, which is also associated with pre-excitation and is characterized by inappropriate deposition of glycogen in the heart. Carling reviewed the functional effects of these mutations and presented data showing that the mutations appear to lead to partial inactivation of AMPK.

In the same session, Dr. Daniel Kelly (Washington University School of Medicine, St. Louis, Missouri) presented data on novel mechanisms possibly underlying the myocardial dysfunction seen in patients with HF, implicating metabolic abnormalities downstream of the peroxisomal proliferator-activated receptor (PPAR)-alpha pathway and "lipotoxicity" in the development of hypertrophy and LV dysfunction. Kelly has found that PPAR-alpha activity is down-regulated in HF. To explore the significance of this, the PPAR-alpha knockout mouse was crossed with a cardiac-specific transgenic mouse overexpressing acyl coenzyme A synthetase. This produced lipotoxicity that was associated with apoptosis, fibrosis, LV dilation, and depressed systolic function. This lipotoxicity could be partially prevented by substituting medium-chain triglycerides for long-chain triglycerides (the normal component of our diet). These data raise the intriguing possibility that manipulation of dietary fat content and of PPAR-alpha activity could potentially alter the progression of HF in patients.

Proteomics. There were two sessions focusing on proteomics, the first of which was jointly sponsored by the National Heart, Lung, and Blood Institute (NHLBI, National Institutes of Health, Bethesda, Maryland) and included speakers from the NHLBI (Dr. John Fakunding) and from four of the proteomics centers recently established by the NHLBI—Boston University School of Medicine (Dr. Wilson Colucci), Medical University of South Carolina, Charleston (Drs. Daniel Knapp and Merry Lindsey), Johns Hopkins University, Baltimore (Dr. Jennifer van Eyck), and Medical College of Wisconsin, Milwaukee (Dr. Andrew Greene), as well as a review of the technology (Dr.

Peipei Ping, UCLA School of Medicine, Los Angeles, California) and a commentary on the proteomics initiative (Dr. Bruce McManus, McDonald Research Lab, Vancouver, Canada). In the second session, Dr. Hayes McDonald (Scripps Institute, La Jolla, California) and Dr. Don Hunt (University of Virginia, Charlottesville, Virginia) reviewed technologic advances in the field that will allow the identification of proteins present at $<10^{-15}$ mol/l concentrations in complex mixtures of proteins (the so-called "shotgun" approach) and will also allow the identification of post-translational modifications of these proteins (e.g., phosphorylation, oxidation). Because so much of a cell's response to stimuli involves post-translational modifications of proteins that are present at very low levels in the cell, the sensitivity of these technologies should allow a much more comprehensive understanding of the range of a cell's responses. Importantly, these approaches take an unbiased approach and do not rely on "candidates" (i.e., one does not need to know what one is looking for before one can look for it). These approaches may well revolutionize the field of proteomics.

Calcium regulation and arrhythmias. This session included talks by Drs. Steven Pogwizd (University of Illinois, Chicago, Illinois), Hector Valdivia (University of Wisconsin, Madison, Wisconsin), and Steven Houser (Temple University, Philadelphia, Pennsylvania), characterizing the cellular alterations in calcium transport and ion channels that contribute to depressed systolic function and triggered arrhythmias seen in humans and animals with HF. A reduced sarcoplasmic reticulum (SR) calcium content (and consequent reduced calcium transients) seems to be a main culprit in systolic dysfunction. This is caused by a combination of reduced SR Ca-ATPase, increased Na/Ca exchange, and increased SR calcium leak. Up-regulation of Na/Ca exchange and depression of potassium currents also increase the propensity for triggered arrhythmias. Dr. Alan Garfinkel (University of California at Los Angeles) showed whole-heart re-entry data and models, indicating how the breakup of stable, spiral waves can occur, even if all cells are identical, and that it depends on the steepness of the restitution of action potential duration versus cardiac cycle length. Finally, Dr. Rui-Ping Xiao (National Institute of Aging, Bethesda, Maryland) showed that there is complex cross-talk between how cAMP- and calcium-calmodulin–dependent protein kinases (PKA and CaMKII) modulate cardiac myocyte function. This session highlighted nicely how understanding the cellular and molecular bases for altered electrophysiologic, calcium transport, and signaling processes in HF may lead to novel molecular targets and therapeutic strategies to combat acute systolic dysfunction and arrhythmias in HF.

Gene therapy. Several presentations in this session offered hope that gene therapy might one day offer novel therapeutic approaches to patients with HF. Recombinant adeno-associated viruses (rAAV) have appeared promising because of their ability to transduce nonreplicating or slowly replicating cells, such as cardiomyocytes, and because they are not human pathogens. Dr. Jude Samulski (University of North Carolina, Chapel Hill, North Carolina) presented studies documenting the different tropisms of various rAAV serotypes. By making use of these tropisms, as well as engineered, cardiac-specific promoters, Samulski showed impressive cardiac transduction achieved through intraperitoneal delivery of such vectors in animal models. Dr. Eduardo Marban (Johns Hopkins University, Baltimore, Maryland) discussed genetic interventions targeted to both bradyarrhythmias and tachyarrhythmias. Proof-of-concept experiments were presented, documenting the ability of vectors to specifically slow atrioventricular (AV) conduction or, alternatively, to restore pacemaker function to cardiomyocytes.

FOCUSED SYMPOSIUM ON DIABETES AND HF

Burden of diabetes and impact on HF. The global increase in diabetes is also affecting HF epidemiology and pathophysiology. A symposium on this new topic was introduced by Dr. Michael Fowler (Stanford University, Stanford, California). Currently, obesity is present in 20% of the U.S. population (defined as a body mass index >30 kg/m^2), and obesity increases the odds of developing diabetes to 3.44:1. In turn, the odds of developing HF is increased fourfold in young diabetic males and eightfold in young diabetic females. Conversely, the incidence of diabetes in HF patients is 20% to 25%.

The associated elevations of serum insulin and insulin growth factor-1 directly predict cardiovascular complications. Conversely, poor HF control also aggravates the diabetic state. The utilization of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers delays the onset or decreases the incidence of new diabetes.

Insulin resistance and diabetic cardiomyopathy. Dr. Dale Abel (University of Utah, Salt Lake City, Utah) discussed insulin resistance and mitochondrial dysfunction in diabetic cardiomyopathy. Normal insulin signaling is required for the metabolic adaptation of the heart to pressure overload, which includes increased glycolysis, glucose oxidation, and expression of GLUT1. Insulin signaling in the heart is impaired in diabetes, and in the context of pressure overload, these hearts develop mitochondrial and metabolic dysfunction and early HF. These observations may explain why diabetes and hypertension are a potent combination leading to rapid development of HF.

HF and PPARs. Dr. Wilson Tang (Cleveland Clinic, Cleveland, Ohio) said that PPAR-gamma plays a distinct role in inhibiting cardiac hypertrophy and attenuates LV remodeling after experimental MI. Thiazolidinediones are PPAR agonists, but have been associated with fluid retention in patients with HF. Indeed, thiazolidinedione users show an increased risk of HF diagnosis, according to the

International Classification of Diseases-9th Revision (ICD-9), from 5.5% to 8.1%, but this is only associated with peripheral edema and actually less pulmonary edema. This risk versus benefit should be carefully weighed in individual patients.

Role of diabetes in acute MI. Dr. Scott Solomon (Harvard University, Cambridge, Massachusetts) demonstrated that the diabetic patient is at increased risk of MI, as well as the adverse consequences of MI, including HF after MI. This risk is independent of the traditional risk factors, including infarct size and ventricular remodeling. The post-MI diabetic patient also develops more fibrosis and worse compliance.

Managing diabetes in the presence of HF. Dr. James Young (Cleveland Clinic, Cleveland, Ohio) suggested that tight glycemic control in patients with HF and diabetes makes the HF easier to control. Each 1% increase in glycosylated hemoglobin is directly associated with an 8% increase in HF. Even if the patient does not have frank diabetes, it is worthwhile to screen for abnormal glucose tolerance in patients with HF, as the prevalence is so high. Aggressive use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or beta-blockers will facilitate the prevention and treatment of HF.

CARDIAC RESYNCHRONIZATION THERAPY (CRT)

How does resynchronization work? Dr. David Kass (Johns Hopkins University, Baltimore, Maryland) demonstrated that ventricular dyssynchrony in bundle branch block actually worsens LV function by requiring a higher local energy expenditure, inducing local molecular and metabolic changes in the high-stress regions of the myocardium. The application of resynchronization provides immediate enhancement of systolic function, thus reducing wall stress and energy cost.

A recent detailed evaluation suggested that the *LV pacing site* has a major impact on the improvement of patients, whereas AV delay and right ventricular/LV timing coupling play a relatively minor role in most patients. Resynchronization is also associated with a reduced degree of mitral regurgitation. Resynchronization enhances the rate of LV pressure rise, thus reducing the effective orifice area, leading to better coordination of papillary muscles and improved chronic chamber remodeling.

New insights from clinical trials. Dr. William Abraham (Ohio State University, Columbus, Ohio) reported that CRT can improve indexes of quality of life, as well as New York Heart Association (NYHA) functional class, as seen in the Multicenter InSync Randomized Clinical Evaluation (MIRACLE), CONTAK-CD, and Multicenter InSync Randomized Clinical Evaluation-Implantable Cardioverter Defibrillator (MIRACLE-ICD) trials. Consistently, CRT improves exercise capacity in trials where this was tested. It also improves cardiac function and structure, with improvement in LV ejection fraction, change in mitral regurgitation jet area, and reduction in LV end-diastolic diameter.

To date, the CRT trials have shown a reduction in hospitalization for worsening HF, but not significantly reduced mortality. Meta-analysis shows that the overall odds ratio for hospitalization was 0.49 (95% confidence interval 0.25 to 0.93), in favor of CRT compared with conventional medical therapy. In the most recently reported Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure (COMPANION) trial, the all-cause mortality at 12 months was reduced by 23.9% ($p = 0.12$) in the CRT group and 43.4% in the CRT with defibrillation (CRT-D) group ($p = 0.002$), as compared with the conventional medical therapy group. In summary, CRT reduces HF and CRT-D reduces morbidity and mortality.

Who is a candidate for resynchronization? Dr. John Parker (University of Toronto, Toronto, Canada) discussed which patients with HF are the most suitable candidates for CRT, in view of the high cost and ancillary resources required for its use. Data from clinical trials to date suggest that patients in NYHA functional class III/IV, with LV ejection fraction <35%, who are already maximized on medical therapy and remain in normal sinus rhythm, are the most ideal candidates. On the other hand, clinical experience also suggests that patients with severe symptoms with recent hospitalization, low blood pressure, dilated LV end-diastolic diameter with mitral regurgitation, high diuretic requirement, and rising creatinine and dyssynchrony on the echocardiogram will likely benefit.

Potential indications that are emerging on the horizon are for patients with HF who need right ventricular pacing for traditional indications or atrial fibrillation and right bundle branch block.

How to look after resynchronization devices. Dr. Leslie Saxon (University of Southern California, Los Angeles) emphasized that attention to details in terms of short- and long-term programming is essential to optimize a clinical response to CRT. This includes lead positioning, rate, and time interval considerations. The pending availability of right-sided hemodynamic monitoring facilities will greatly improve the ease with which these devices are followed.

Is there still a role for the traditional pacemaker? Dr. Tony Tang (University of Ottawa, Ottawa, Canada) discussed the issue of what to do with HF patients who require pacing according to traditional indications. If the HF patient needs a pacemaker because of bradycardia, and if the patient has good AV conduction, then either the VVI or DDD/R mode will do. However, if AV conduction is poor, then the DDD/R mode will be required. If the patient has atrial fibrillation but needs only backup pacing, then the VVI/R mode may be sufficient. However, if the patient is being paced most of the time, then CRT with biventricular pacing will be much more appropriate.

CLINICAL TRIALS

There were a number of new or updated clinical trials presented at the meeting; only two with data not presented before at an international forum are summarized here.

The TEN-HMS trial. The purpose of the Trans-European Network-Home Management System (TEN-HMS) trial, presented by Dr. John G. F. Cleland (University of Hull, Kingston-Upon-Hull, United Kingdom) is to compare three different strategies for following HF patients who have been recently discharged from the hospital. They were randomized to either: 1) usual care (traditional physician-based program); 2) nurse telephone service (monthly nurse telephone call plus usual care); or 3) home telemonitoring with patient-initiated recording of blood pressure, weight, and electrocardiographic recording with automatic transmission of data via a modem to a care team twice per day.

The primary outcome of the study was days lost to death or hospitalization. The secondary end points were death, hospitalization, or changes in medications. Ultimately, 85 patients were randomized to the usual care group, 173 patients to the nurse-managed care group, and 168 patients to the device-monitored group. At baseline, 60% of the patients were in NYHA functional class I or II (mean age 67 years, mean LV ejection fraction 25%).

The percentage of days in which the patients were dead or hospitalized was reduced from 19.5% with usual care to 15.9% for nurse-managed care and 12.7% for the combined device- and nurse-managed care groups. There was also an absolute reduction of 16.4% in mortality when comparing the intervention versus usual care groups ($p < 0.05$). The mean duration of hospitalization was reduced from 17.5 days with nurse telephone support versus 11 days with telemonitoring ($p < 0.05$). Patients in the telemonitoring group were more likely to have evidence-based medications successfully implemented than were patients in either of the other groups. Therefore, the investigators concluded that increased patient support and monitoring reduced mortality, and when compared with usual care, the monitoring device strategy reduced hospital length of stay and days lost due to death or hospitalization and was also associated with lower costs.

The RED-HOT trial. The Rapid Emergency Department Heart Failure Outpatient Trial (RED-HOT), presented by Dr. Alan Maisel (San Diego VA Healthcare System, San Diego, California) was designed to evaluate the prognostic and triage role of point-of-care brain natriuretic peptide (BNP) determination in the emergency room in triaging a patient presenting with suspected HF, as compared with the physician's judgment alone. The hypothesis is that BNP determination may fare better than clinical judgment.

In the RED-HOT study, 464 patients presenting with dyspnea to the emergency department with suspected HF were enrolled. Patients with BNP <100 pg/ml, MI, or renal failure were excluded. The BNP level was determined on arrival and thereafter every 3 h, but the attending physicians were blinded to the values.

The patients' average age was 63 years; 54% were males and >50% were African-Americans. The physician-perceived clinical status was used to categorize 76% of the patients as being in NYHA functional class III/IV, but 90% were ultimately admitted. There was a significant discrepancy in the physician's assessment versus BNP measurements. For example, 11% of the patients were admitted with actual BNP values <200 pg/ml, yet 66% were perceived by the physician to be very sick. In contrast, in the patients with BNP >200 pg/ml, 76% of those were perceived to be very sick.

On follow-up, those patients who had initial BNP <200 pg/ml had 0% and 0% mortality at 30 and 90 days, respectively. However, those who had BNP >200 pg/ml accrued 4% and 7% mortality at 30 and 90 days, respectively. The average BNP values were 976 pg/ml in those who were discharged versus 767 pg/ml in those who were admitted. At 30 days, those who were alive had an average BNP value of 764 pg/ml, as compared with an initial value of >2,000 pg/ml in those who died.

The investigators concluded that patients with initial BNP values <100 pg/ml can be discharged home, whereas those with BNP values between 100 and 400 pg/ml should be considered for emergency department treatment, followed by discharge if clinically stable.

SUMMARY

In addition to the sessions highlighted herein, the meeting included debates, "how to" sessions, young investigator award competitions, late-breaking clinical trials, case discussions, bench-to-bedside sessions, as well as moderated poster and regular poster sessions. The next Annual Scientific Meeting of the Heart Failure Society of America will be held September 12 to 15, 2004, in Toronto, Canada (http://www.hfsa.org).

Reprint requests and correspondence: Cheryl Yano, Executive Director, Heart Failure Society of America, Court International Suite 240 South, 2550 University Avenue West, St. Paul, Minnesota 55114. E-mail: cyano@hfsa.org.